Boffin Access

Open Access Journal | Volume: 1.2

International Journal of Clinical and Medical Cases

ISSN 2517-7346

Novel Therapeutic Options for Prevention and Treatment of Peptic Ulcer Disease

Ihekwereme Chibueze[1*]
Umeh N.Victoria[1]

[1*]Department of Pharmacology and Toxicology, Nnamdi Azikiwe University Awka, Anambra state Nigeria

Abstract

Gastrointestinal (GI) toxicity associated with non-steroidal anti-inflammatory drugs (NSAIDs) is still an important medical and socio-economic problem – despite recent pharmaceutical advances. Furthermore, no monotherapy has been able to eradicate Helicobacter pylori bacteria which have been reported to be the major cause of peptic ulcer disease. In recent time, a lot of attention has been focused in developing new treatment and preventive options for peptic ulcer disease. This review also illustrates the current status of the available techniques in endoscopy with a focus on screening for peptic ulcer disease. There is the need for the review of these recent approaches and breakthroughs hence, this literature review.

Keywords

COX/5-LOX; *H. pylori*; Prevention; NO-NSAID; NSAIIDs; Modern endoscopy

Introduction

Peptic ulcer diseases comprise heterogeneous disorders, which manifest as a break in the lining of the gastrointestinal mucosa bathed by acid and pepsin. It is the most predominant of the gastrointestinal diseases with a worldwide prevalence of about 40% in the developed countries and 80% in the developing countries [1,2]. It is generally recognized that peptic ulcer is caused by a lack of equilibrium between the gastric aggressive factors(acid-pepsin secretion, parietal cell) and the mucosal defensive factors (mucosal barrier, mucus secretion, blood flow, cellular regeneration and endogenous protective agents e.g prostaglandins) [3] Figure 1.

It is a well-known phenomenon that non-steroidal anti-inflammatory drugs (NSAIDs) cause gastric mucosal damage. Topical damage caused by NSAIDs includes the accumulation of ionized NSAIDs in the gastric epithelial cell called 'ion trapping' effect, the reduction of the hydrophobicity of the gastric mucosal surface and uncoupling of oxidative phosphorylation [4-6]. Disruption of the epithelial barrier allows back-diffusion of acid into the mucosa. Since the identification of H. pylori as a causative agent in peptic ulcers by Barry Marshall and Robin Warren in the late 20th century, the gastroenterological practice worldwide has changed [7]. However, only a combination of antimicrobials can be used in vivo to eradicate H. pylori and none of the antimicrobials is effective enough to eliminate H. pylori when given as monotherapy [8]. Helicobacter pylori infection is reported to account for more than 70% of cases of peptic ulcer diseases [9]. Currently the pathogenic effect of the peptic ulcer disease due to recurrence after cessation of the treatment is yet to be resolved. The emergence of antibiotic resistance, the high cost of the currently available treatment measures, and the increase in the number of reported relapses highlight the need for new alternative therapeutic approaches [10]. New treatment and preventive strategies for peptic ulcer disease are steadily being discovered, adopted and evaluated in clinical studies with very promising results. They include strategies for the prevention of NSAIDs-induced upper digestive injury, maintenance of gastric mucosal balance, development of nano bodies against UreC subunit of urease enzyme and research towards vaccine development against H. pylori bacteria.

Prevention of NSAIDS-Induced Gastrointestinal Damage

NSAIDs are known to cause gastrointestinal (GI) toxicity that often leads to ulceration or perforation of the GI mucosal lining, a factor that limits their use. The major concern with the chronic usage of aspirin or other NSAIDs is that 30 to 40% of patients using NSAIDs have a GI intolerance to the drugs and suffer from a spectrum of symptoms ranging from dyspepsia to peptic ulcer disease, the latter which may be associated with life-threatening episodes of hemorrhage [11]. One clinical study demonstrated that 30% of chronic NSAIDs users had at least one gastroduodenal ulcer, as observed via endoscopy [12]. Furthermore, a retrospective study restricted to rheumatoid arthritis patients in the U.S. concluded that GI complications as a result of NSAIDs usage are responsible for 400,000 hospitalizations and 16,000 deaths annually in this patient population [12]. At present, novel pharmacological

Article Information

DOI:	10.31021/ijcmc.20181109
Article Type:	Review Article
Journal Type:	Open Access
Volume:	1 **Issue:** 2
Manuscript ID:	IJCMC-1-109
Publisher:	Boffin Access Limited
Received Date:	March 29, 2018
Accepted Date:	April 21, 2018
Published Date:	May 02, 2018

*Corresponding author:

Ihekwereme Chibueze
Department of Pharmacology and Toxicology
Nnamdi Azikiwe University Awka
Anambra state Nigeria
Phone: 08034049012
E-mail: cp.ihekwereme@unizik.edu.ng

Citation: Chibueze I, Victoria UN. Novel Therapeutic Options for Prevention and Treatment of Peptic Ulcer Disease. Int J Clin Med Cases. 2018 Apr:1(2);109

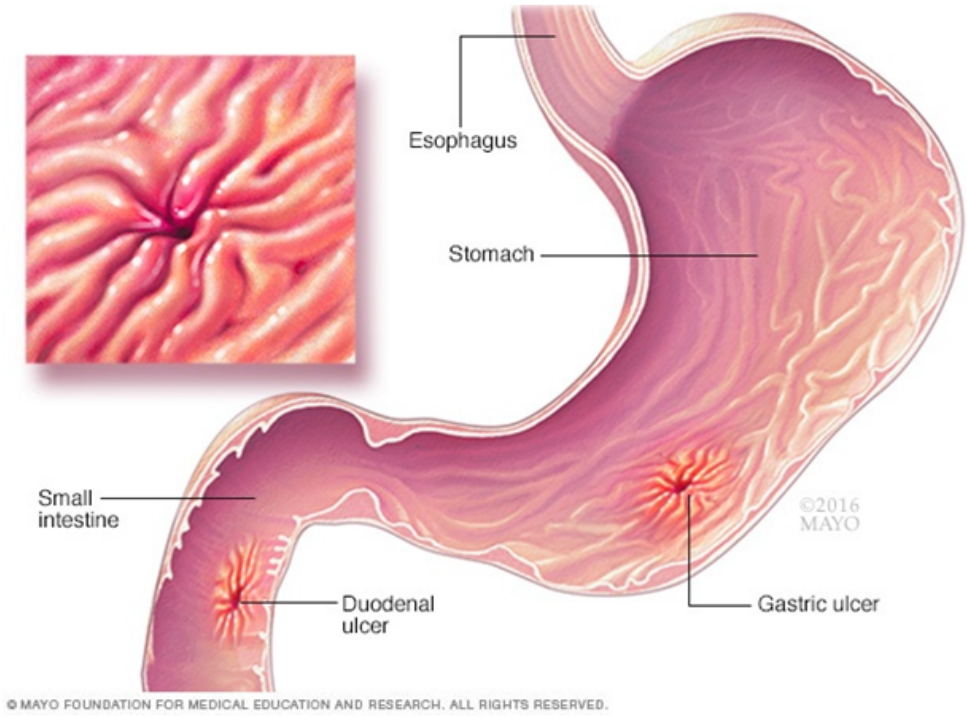

Figure 1: Schematic diagram of Peptic ulcer disease manifestations

strategies are being investigated to counteract the detrimental actions of traditional NSAIDs on the gastrointestinal tract. The main options currently under active evaluation are the formulation of fixed combinations of NSAIDs with a gastro protective drug.

Traditional NSAIDS Associated with Phosphatidylcholine (PC)

PC is the most active form of gastric phospholipids which protects the gastro-intestinal track (GIT) from ulcerogenic conditions or compounds including NSAIDs. NSAIDs such as aspirin disrupt the natural barrier mechanism of the gastric epithelium because they bind to the mucosal surfactants (phospholipids). When NSAIDs associate with surface phospholipids the hydrophobic barrier becomes hydrophilic allowing acid to permeate the mucosal lining resulting in disruption of mucosal integrity [13] (Figure 2). Exogenous Phosphatidyl-choline is a functional excipient that plays a key role as a solubilizing agent via the formation of a non-covalent complex with the active ingredient NSAID. By association with the active ingredient, the PC-NSAID complex becomes markedly more lipophilic [14]. This enhanced lipid solubility of the drug promotes its transit across the hydrophobic mucus gel layer of the upper GI tract, presumably the stomach, with reduced surface mucosal injury. The PC- containing oil excipient neither impedes the bioavailability of the NSAID nor changes the pharmacological activity. The PC lipid based NSAID products currently being developed by Plx Pharma offer lower risk of gastrointestinal erosion and ulceration while maintaining the pharmacological activity and bioavailability demonstrated by the commercial NSAID drug products [15]. Thus this new class of PC associated NSAIDs appears to offer lower risk of GI erosion and ulceration while maintaining the pharmacological activity and bioavailability demonstrated by the commercial NSAID drug products.

Biliary NSAIDs Associated with Phosphatidylcholine (PC)

NSAIDs are rapidly absorbed from the GIT and in many cases undergo enterohepatic circulation. Bile plays important role in the ability of NSAIDs to induce small intestinal injury. Bile acids are synthesized in the liver. Bile salts (conjugation of bile acid and taurin or glycin) are known to destroy the permeability barrier of gastric mucosa and increase mucosal permeability to acids. Biliary PC is important in detoxification of bile salts. NSAIDs that are secreted in the bile injure the intestinal mucosa by their ability to chemically associate with biliary PC which forms toxic mixed micelles and limits the concentration of biliary PC available to interact with and detoxify bile salts. Thus NSAIDs with extensive entero-hepatic cycling are more toxic to GIT and are capable of attenuating the surface hydrophobic properties of the mucosa of lower GIT. Hence, pre associating the NSAIDs with exogenous PC prevents a decrease in the hydrophobic characteristics of the mucus gel layer [16].

Nitric Oxide (NO) Donating NSAIDs

These classes of NSAIDs have been developed exploiting the concept that NO released locally in the gastric mucosa, would enhance the mucosal blood flow and reduce leukocyte adherence in the gastric microcirculation. This new class of NO-NSAIDS is prepared by adding a radical, nitro butyl or nitrosothiol by using a short chain ester linkage. This exhibits reduced gastrointestinal toxicity while enhancing vasodilatation, reducing blood platelet adhesion and acting as a buffer against memory loss [17]. They are synthesized by ester linkage of a NO- releasing moiety to conventional NSAIDS, such as aspirin (NO-Aspirin), flurbiprofen (NO-flurbiprofen), naproxen (NO-naproxen), diclofenac (Nitrofenac), lbuprofen (NO-lbuprofen) and indomethacin (NO-indomethacin). An experimental study with NO-NSAID showed their ability to spare the gastrointestinal tract after either acute or chronic use in animals; NO-naproxen is completely devoid of ulcerogenic activity [18]. Similar results have been reported with NO-Aspirin after single dose administration in rats, Nitrofenac, NO-indomethacin [19-22]. The capacity of NO-NSAID to release NO appears to affect the gastrointestinal toxicity [22]. NO-aspirin accelerated the healing process; NO-aspirin showed a dose dependent decrease in the severity of HCl/ethanol induced stomach lesions in rats [23]. NO-NSAID may be valuable in the treatment of existing ulcers and are likely to be of greater therapeutic benefit than classical NSAID for the treatment of inflammatory disease in patients with pre existing gastric damage. COX inhibiting NO-donating drug (CINOD) inhibits COX-1 and COX-2 activities, has less adverse effect on gastrointestinal tract and reduces systemic blood pressure. NO-ASA (Acetyl Salicylic Acid) maintains gastric mucosal blood flow and reduces leukocyte – endothelial cell adherence [22]. A recently

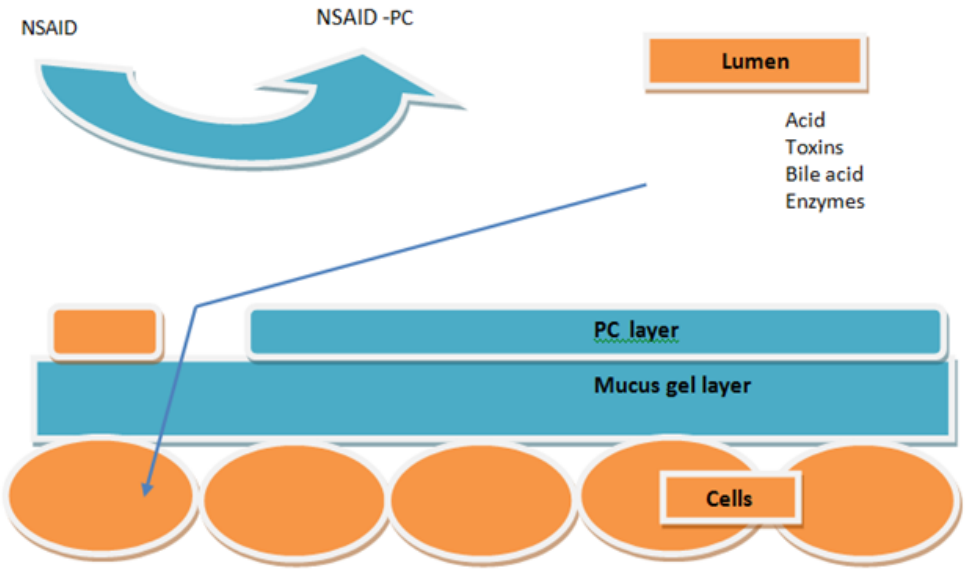

Figure 2: The mechanism by which non-steroidal anti-inflammatory drugs (NSAIDs) may compromise the surface barrier by disrupting the PC layer allowing luminal agents access to the epithelium.

published study involving a total of 31 volunteers supported the data obtained in animal studies showing significantly reduced but not completely abolished GI toxicity associated with NO-naproxen compared with conventional naproxen in humans [24].

NSAIDs Releasing Hydrogen Sulfide (H2S)

Hydrogen sulfide (H2S) is a gaseous mediator actively involved in the maintenance of digestive mucosal integrity and blood flow [25]. This gaseous compound, previously regarded as a toxic agent, is emerging as an endogenous modulator which seems to share almost all the beneficial actions of NO on several physiological processes. In particular, it has been demonstrated that H2S is produced by the gastric mucosa, and that it contributes to the ability of this tissue to resist damage induced by luminal agents [26]. Interestingly, several lines of evidence have shown that H2S donors can prevent the decrease in gastric blood flow induced by NSAIDs and reduce NSAIDs-induced leukocyte accumulation and adhesion in gastric micro vessels, thus providing a rationale for the synthesis of H2S-releasing NSAID derivatives as novel anti-inflammatory drugs [26]. As previously observed with CINODs, an H2S-releasing derivative of diclofenac was shown to be better tolerated in terms of gastric damage as traditional NSAIDs and the addition of the H2S- releasing moiety has been found to increase the anti-inflammatory activity of diclofenac. Additional strategies for the prevention of NSAID-induced upper digestive damage include the ongoing clinical development of pharmaceutical products containing fixed combinations of NSAID with a gastro protective drug, such as naproxen/omeprazole, naproxen/lansoprazole, naproxen/esomeprazole and ibuprofen/famotidine [25].

Addition of Anti-Oxidant/Vitamin C

Both vitamins C and E seem to play a role in the preservation of gastric mucosal integrity; vitamin C is actively secreted into the gastric lumen of healthy subjects and its concentrations are decreased in patients with gastroduodenal diseases such as peptic ulcer disease and gastric malignancy [27]. The underlying molecular mechanisms, however, are not fully understood. The activity of protective anti-oxidizing enzymes like superoxide dismutase and glutathione peroxidase, intragastric vitamin C levels in the stomach were impaired by Asprin [28]. Co-medication with vitamin C abolished these effects, was able to scavenge free radicals, and significantly attenuated gastric damage [28]. It has been recently shown that the gastroprotective effects of vitamin C as observed in humans might at least in part be mediated by haeme-oxygenase-1 (HO-1) [29]. HO-1 is ubiquitous and crucial tissue-protective enzyme with vasodilative, anti-inflammatory and antioxidant properties. Vitamin C has been identified as a potential non-stressful inducer of HO-1 in the stomach [30].

The Use of Dual Inhibitors of Cox and 5-Lox Enzymes

The development of osteoarthritis may be accompanied by increased production of leukotrienes (LTs) and prostaglandins (PGs) from arachidonic acid. These products contribute to joint damage, pain and inflammation. Cyclooxygenase, COX-1 and COX-2 are responsible for the production of PGs. Inhibition of these enzymes by non-steroidal anti-inflammatory drugs and selective COX-2 inhibitors reduce the levels of PGs, resulting in a reduction in pain and inflammation. This inhibition can cause alternative processing of arachidonic acid via the 5-lipoxygenase (5-LOX) pathway, resulting in increased production of proinflammatory and gastrotoxic LTs. Hence dual inhibitors of COX/5-LOX have been developed in order to achieve enhanced anti-inflammatory activity while sparing gastric mucosa [31]. Licofelone (or ML3000) was demonstrated to exhibit these properties in animal trials [31]. Licofelone is a competitive inhibitor of 5-LOX, COX-1 and COX-2 that is currently being developed for the treatment of osteoarthritis. Licofelone decreases the production of both LTs and PGs, and thereby reduces inflammation and pain with low gastro toxicity. Unlike selective COX-2 inhibitors, co administration of licofelone and aspirin does not appear to be associated with an increase in gastrointestinal adverse events, at least under experimental conditions. Furthermore, there is evidence from animal models to suggest that Licofelone may stop disease progression [32]. Phase II trials have indicated that this COX/5-LOX inhibitor spares human gastric mucosa Licofelone has been shown to retain its GI safety profile when taken together with low-dose aspirin in a study involving 75 patients [33,34].

Maintenance of Gastric Mucosal Balance

Peptic ulcer disease is caused by a lack of equilibrium between the gastric aggressive factors and the mucosal defensive factors [35]. The various aggressive factors include bile, bacteria, enzymes,

pepsin-HCL secretion and defensive factors include mucosal barrier, mucus secretion, blood flow, cellular regeneration, bicarbonate and endogenous protective agents (prostaglandins and epidermal growth factors [3]. When the latter cannot keep up with the former, the stage is set for stomach wall disruption and ultimately ulceration. Though it is logical to focus on reducing acid production and eliminating *H. pylori*, the question remains as to why the mucosal lining was compromised in the first place. Given that many more individuals carry *H. pylori* than have ulcer disease, it is clear that other factors influence the onset of the disease process. Even with the best pharmacotherapy, ulcer recurrences are common, suggesting that acid suppression and eradication of microbial pathogens is insufficient. The current therapeutic challenge is to restore the delicate balance by addressing the factors that impair healing of the gastric lining, and improving mucosal integrity. Zinc carnosine was developed in an effort to close that gap, by providing a therapy that bolsters the ability of the gastric lining to repair and protect itself. Carnosine is a naturally-occurring dipeptide, comprised of β-alanine and L-histidine. It is a chelate of elemental zinc and car nosine in a 1:1 ratio. It is a strong free-radical scavenger capable of blocking free radical chain reactions, thus inhibiting lipid peroxidation [36]. H. pylori cannot survive at low pH without producing urease which catalyzes the hydrolysis of urea to ammonia and CO_2. In the stomach, the organism creates an ammonia-rich "bubble" which neutralizes gastric acid, allowing it to embed in the gastric epithelium. To date, there have been 8 clinical trials of zinc carnosine for the treatment of peptic ulcers [37]. It is marketed in Japan under the trade name of Polaprezinc and in the US it is marketed as ZinLori 75 in tablets and capsules by Metagenics.

Vaccine Formulations against H. Pylori Bacteria

Helicobacter pylori infection of the gastric mucosa remains a cause of significant morbidity and mortality almost 30 years after its discovery [7]. The vast majority of H. pylori infections are acquired during childhood and the most frequent route of infection is oral-to-oral transmission [38]. Unless successfully eradicated either by anti microbial treatment or via host inflammatory and immune responses, most infections persist for life. In developed countries, it has been calculated that a 10-year vaccination program would significantly reduce the prevalence of H. pylori-related peptic ulcers and gastric cancer in the population and related morbidity and economic costs associated with these diseases [39]. For these reasons, research towards a vaccine against H. pylori infection for use in humans has been ongoing since shortly after the isolation of H. pylori in 1984 [7]. Numerous vaccination studies have now been performed in rodents using either Helicobacter felis or H. pylori as challenge organisms [40]. H. felis lacks many of the virulence mechanisms identified in H. pylori but it induces significant levels of histologic gastritis and has many features resembling H. pylori-induced gastritis in the human stomach. Survey of studies of candidate vaccines reveals that it is possible to induce some level of immunity against H. felis or H. pylori infection by use of any one of various vaccination strategies [41]. Significant reductions in bacterial load have been achieved in vaccinated mice following challenge of their immune system with H. pylori or H. felis organisms [42].

Clinical Trials

Clinical trials with prototype H. pylori vaccines began at about the same time as some of the nonhuman primate studies. Given the nature of most of the animal model studies performed during the 1990s, these clinical trials have predominantly focused on H. pylori urease-based vaccines delivered orally. The first clinical trial tested the therapeutic efficacy of an *H. pylori* vaccine administered to *H. pylori*- positive individuals [43]. 180 mg, 60 mg, or 20 mg doses of *H. pylori* urease were administered in combination with either 5 μg or 10 μg according to an immunization and booster regime previously shown to be successful in mice. Immunogenicity was determined by measuring the number of urease-specific antibody-producing cells in the blood. Disappointingly, no sterilizing immunity was observed in vaccinated individuals, but a significant reduction in bacterial load was observed in individuals given the 20 mg dose of *H. pylori* urease. Gastric inflammation was unaltered by vaccination. However, when the results of these studies are combined, some important summations can be made that may be applicable to humans:

- Immunity can be induced through the use of any one or a combination of the following H. pylori antigens; inactivated whole cell preparations, H. pylori proteins such as the urease enzyme, cytotoxin-associated gene a product (Caga), vacuolating toxin a (vaca), catalase, heat shock protein. All above have been shown to confer immunity against gastric H. pylori infection [42].
- Immune protection can be induced by many different routes of mucosal vaccination including orogastric, intranasal, and rectal [44].
- Finally, studies in mice have demonstrated that immunity to H. pylori infection relies more on developing a strong t-helper-cell (tH)-dependent cellular inflammatory response than on a humoral immune response [45].

Though the results of the clinical trials are disappointing, new vaccine strategies against H. pylori are being designed to bypass or override the host immunoregulatory response [46]. It may provide the best opportunity to develop an efficacious vaccine against H. pylori

Development of Nanobody against Urec Subunit of Urease Enzyme

Urease is a nickel-containing enzyme found in H. pylori that catalyzes the hydrolysis of urea to ammonia and carbon dioxide in the acid environment of the stomach [47]. The products of this reaction, bicarbonate and ammonia, are strong bases that further protect the bacteria from the stomach acid because of their acid-neutralizing capability.

urea + stomach acid + water ⟶ bicarbonate + ammonia

$$C{=}O{\bullet}2NH_2 + H^+ + 2H_20 \longrightarrow HCO_3 + 2NH_4^+$$

The enzyme Urease therefore plays an important role in the infection capabilities of H. pylori. It allows this pathogen to survive, grow, and multiply at the low pH of the stomach, spreading infection to the inner layers of gastro duodenal mucosa, resulting in gastritis and peptic ulceration, which in some cases leads to gastric cancer [48]. Urease constitutes 10–15% (w/w) of the total proteins produced by H. pylori, and presents in both the cytoplasmic and surface-associated forms [49].

UreC is one of the urease enzyme subunits. UreC is an antigenic protein that can stimulate a specific and innate response and contains an enzyme active site [50]. Nanbody is a single domain antibody (sdAb) fragment consisting of a single monomeric variable antibody domain. These antibodies have a single chain variable domain referred to as VHH or sdAb or nanobody. Like a whole antibody, it is able to bind selectively to a specific antigen. Nanobodies have better tissue penetration and effective pharmacodynamics with less interference with the host immune system [51]. The greater therapeutic value of nanobodies over conventional antibodies is due to their small size (2.5 nm in diameter and nearly 4 nm high) high stability at extreme temperatures and PH, physical stability, capability of refolding and binding to unique epitopes inaccessible to conventional antibodies [52]. The administration of antibody against H. pylori is a new effective therapeutic strategy. Based on previous research [53]. UreC-specific antibodies can neutralize H. pylori urease enzyme and reduce bacterial colonization in an invitro environment [53]. Antibodies, unlike antibiotics, can recognize certain antigens on the microorganism and neutralize virulence factors that enable the host immune system to interact with the microorganism and furthermore prevent relapses [54]. Several nanobodies against urease enzyme have been produced [55]. But due to problems such as low stability and low yield of production and immunogenicity, the need for a new generation of antibodies seems necessary [56]. A novel single-variable domain of heavy chain antibody against recombinant UreC has been successfully developed [57]. This particular work is an improvement over previous work in this field in the following areas:

- The affinity of this monoclonal antibody against UreC recombinant protein is higher in comparison with the previous reports [56].
- Nanobodies unlike conventional antibodies can recognize epitopes such as cavity and cleft in the active sites as they have a convex paratope or antigen–binding site [58]. This nanobody has advantages over those of previous studies in this respect.
- Furthermore the stability tests of this nanobody revealed high thermostability and resistance to denaturing agents and proteolytic enzymes [57]. The resistance to proteolytic enzymes is of significant importance in the oral administration of anti-H. Pylori antibodies. This characteristic allows the oral administration of this antibody in the treatment of stomach ulcer without any loss of binding activity.
- This nanobody showed resistance to thermal denaturation and the retention of full activity after incubation at high temperatures [57]. This property increases the antibody's shelf-life.
- The results of the urease inhibitory test showed that this nanobody can successfully inhibit the surface urease activity of H. pylori. This can significantly reduce bacterial survival in acidic environments such as the stomach [56].

Hence nanobody could be a great therapeutic strategy for the eradication of H. pylori infection considering its advantages over conventional antibody.

Challenges of New Anti-Ulcer Development

The growth of peptic ulcer disease with time is complex and interesting. Although its incidences were rare before 1800 century, with time and change in life style its incidences have increased significantly [59]. Several therapeutic strategies have evolved over time for its management. Research for development of antiulcer agents usually aims to address one or more of these factors (pepsin-HCL), muscarinic -M1 receptors, gastrin receptors, histamine-H2 receptors and proton pumps, analogues of prostaglandins, mucosal protection and eradication of H. pylori. Considering the involvement of multiple factors in its etiology, it has not been possible to provide an ideal solution to completely cure peptic ulcer disease occurrence. Traditional use of antacids and use of histamine inhibitors have become insufficient in the management of peptic ulcer. Irreversible inhibition of proton pump although reduces ulceration in the long run leads to adverse issues. It has not been possible to develop an ideal proton pump inhibitor. In this scenario, search for alternatives by capitalizing on the multifactorial etiology of ulceration holds promise. However, these searches are far from over and require further investigations to develop ideal antiulcer agents. Moreover, application of some of the new strategies is still limited due to lack of research for several reasons. Such reasons being that the prevalence of peptic ulcer disease in Western countries is low (limited access to volunteer participants for clinical trials), the high costs of performing such studies on a large scale in developing countries where there is high prevalence of infection is high and there is inadequate facilities to carry out these clinical trials studies in these countries.

Modern Methods of Endoscopy

Endoscopy is a procedure in which an instrument is introduced into the body to give a view of its internal parts. Rapid advancements in computer and chip technology and the resulting technical options in imaging and image processing have influenced modern endoscopy today as never before in the past. A large number of technical innovations have been introduced in diagnostic endoscopy in the last few years, with the aim of improving the detection and characterization of pathological changes in the gastrointestinal track. High-resolution image display in endoscopes of the newest generation is supported by virtual chromoendoscopy, a type of staining of mucous membranes at the press of a button. Classical chromoendoscopy is also significant for specific indications. Recent microscopic procedures such as endomicroscopy and endocytoscopy are able to not only predict pathological changes on the basis of their surface or vascular pattern, but also directly visualize the cellular architecture of the mucosa. The better the quality and clarity of images, the better the patient can be cared for. Thus, the main purpose of endoscopy can be achieved, which is early and timely detection of peptic ulcer disease.

High Definition Endoscopy

High definition became a catchword after the introduction of high definition television (HDTV) in television and entertainment technology. It produced high-resolution images that were practically incomparable with, and unobtainable by, the previously used transmission technology (PAL) in endoscopy. Further development of chip technology (CCD chip), by which more than one million pixels per image can be analyzed today, led to the achievement of much greater resolution in so-called high-resolution endoscopy than in video endoscopy of the first generation [60]. The most recent color chips, although miniaturized, currently permit greater pixel density and a resolution of more than one million pixels per video image, which can now be visualized by the new television standard of HDTV [60]. This has greatly enhanced image quality compared to standard resolution (SR). Combined with conventional or virtual chromoendoscopy, preliminary clinical data indicate that the technical advancement of HD endoscopy is a decisive element of better diagnostic investigation, and is thus able to exert an immediate impact on the prognosis of the disease for patients [61].

Chromoendoscopy

The color dyes or pigments used in chromoendoscopy either react with intracellular structures of mucosa (absorption) or remain on the mucosal surface (contrast stain).The most commonly used staining materials in the upper gastrointestinal tract are Lugol's solution (changes in squamous epithelium) and acetic acid (changes in the columnar epithelium). In the lower gastrointestinal tract one usually employs indigo carmine or methylene blue [62]. The somewhat greater expenditure of time and the large number of available staining materials, as well as uncertainty about the quantity and concentration of staining materials have prevented chromoendoscopy from being established in the Western world. However, the knowledge of the morphology of the diseases of the upper and lower gastrointestinal tract has been enhanced very markedly by the use of chromoendoscopy, and has sensitized clinicians to the necessity of early detection, particularly that of flat lesions [63]. Chromoendoscopy is currently experiencing a renaissance because the combination of high-resolution endoscopy and intravital staining provides an especially detailed view of the surface structure of mucosa.

Virtual Chromoendoscopy

Owing to the previously described modern processor technology of high-resolution endoscopy systems and the possibility to add color by pressing a button and activating a color filter, virtual coloring is currently receiving special attention in endoscopy. The procedure of so-called virtual chromoendoscopy modulates, by the press of a button and with no loss of time, the spectrum of visible light so that the mucous membranes can be visualized in various "missing colors" [60]. The effect of such color accents is that individual components of the mucosa, such as the surface pattern or vascular structures of the mucous membranes can be depicted more clearly [61]. The different color spectrums are produced either by modulating the incoming light with filters (NBI technique), or by software-based processing (so-called post-processing) of the reflected light (FICE, i-scan technique or SPIES) [61]. Thus, modern filter technology is replacing, to an increasing extent, the more time-consuming procedure of chromoendoscopy.

Iscan, Fice and Spies

The filters i-scan (Pentax, Europe), SPIES (Karl Storz, Europe) and FICE (Fujinon, Europe) are based on processor-integrated software applications that alter the wavelength ranges of reflected light and thus, in contrast to NBI technology, offer a number of filter options [61]. In addition to depicting vessels, portions of tissue and surface structures can be visualized in a selective and accentuated

manner. I-scan technology is based on an integrated software tool that enhances the surface with the aid of the function of "surface enhancement" and, by additionally switching on specific color filters, permits virtual chromoendoscopy to be performed. Initial published studies have confirmed the efficacy of this procedure. Thus, reflux lesions in the upper gastrointestinal tract (UGI) could be diagnosed more accurately by the use of surface enhancement [64]. FICE (Fujinon Intelligent Color Enhancement System) and SPIES (STORZ Professional Image Enhancement System) are other types of computer-assisted virtual chromoendoscopy.

Auto fluorescence and Spectroscopy

Autofluorescence endoscopy is another advancement in endoscopy, which is playing an increasingly significant role in the early detection of gastro intestinal damage. The principle of fluorescence diagnosis is based on the fact that light of a specific wavelength (approximately 400-500 nm) is not merely absorbed and reflected in tissue, but also causes fluorescence produced by auto fluorophores or exogenously introduces fluorophores [65]. A variety of pathological processes such as inflammation, ischemia, and adysplasia demonstrate different fluorescence behavior compared to normal tissue. Therefore, this technology is also known as red flag technology. However, a disadvantage of the method is the fact that autofluorescence is associated with a high rate of false positive diagnoses. To enhance the specificity of this method, it is usually combined with HD endoscopy and NBI for characterization of the detected lesions; this is known as endoscopic trimodal imaging [66].

Molecular Imaging

Molecular imaging gives rise to early detection of disease condition of gastro intestinal track because it renders pathological changes visible at the cellular level [67]. The optic form of molecular imaging, which provides colored views of suspicious areas on the endoscopy image, can already be used in vivo for various types of tumors. By the use of molecular probes usually applied exogenously, one can visualize specific surface molecules or metabolic processes that occur selectively in the target tissue. Thus, by marking antibodies to epitopes like the epidermal growth factor receptor (EGFR) or the vascular endothelial growth factor (VEGF); this was achieved in mouse models as well as in human tissue. The advantage of antibodies is their highly specific binding to their target structure, which causes marked contrast between (stained) diseased and (non-stained) healthy tissue. Molecular imaging requires special endoscopes that either permits the detection of lesions on the overview image or microscopic characterization of molecular processes during endoscopy. As a result, the use of molecular imaging for endoscopy has not been established in large patient populations, but is very likely to fundamentally influence future clinical algorithms and has already brought about a significant advancement in clinical and basic research by enhancing our comprehension of gastrointestinal diseases.

Conclusion

The prevalence of antibiotic-resistant by H. Pylori strains, the high cost of treatment, and the risk of relapse, have led to the need for a new approach to the treatment of H. pylori-related diseases. Use of NSAIDs-PC, NO-NSAIDs, H2S-NSAIDs formulations, maintenance of gastric mucosal balance, development of nanobody and vaccination are potential options for the treatment and prevention of peptic ulcer disease. NO-NSAIDs represent a promising therapeutic alternative to conventional COX1and COX-2 selective NSAIDs. NO-NSAIDs not only reduced profile of GI side-effects but also ameliorated power of desired effects. Large, randomized studies are needed to evaluate definitively the clinical benefit of NO-NSAIDs in humans. Therefore, all levels of research, including basic, clinical, and population-level, need continued support to facilitate development and implementation of these novel breakthroughs. In addition to the fact that simultaneous histological investigation can be performed along with endoscopy, some diseases can now be diagnosed reliably for the first time, and physiological as well as pathophysiological processes can be observed. This development has caused molecular imaging to gain center stage in endoscopy. Apart from the fact that it has simplified better detection of suspicious lesions, oncological therapy approaches can be planned and understood better. Although gastrointestinal endoscopy has become much more complex now, the optic details provided by the new technologies will contribute significantly to improving the efficiency of the diagnosis and treatment of gastrointestinal endoscopy.

References

1. Gregory MC, Tolman KG. Diseases: Manifestation and Pathophysiology, In: Remington. The science and Practice of Pharmacy. 20th ed.1991;2:1084-1085.
2. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet. 2009 Oct;374(9699):1449-1461.
3. Rao CV, Sairam K, Goel RK. Experimental evaluation of Bocopa monniera on rat gastric ulceration and secretion. Indian J Physiol Pharmacol. 2000 Oct;44(4):435–441.
4. Davenport HW. Salicylate damage to the gastric mucosal barrier. N Engl J Med. 1967 Jun;276(23):1307-1312.
5. Lichtenberger LM. The hydrophobic barrier properties of gastrointestinal mucus. Annu Rev Physiol. 1995;57:565-583.
6. Jörgensen TG, Weis-Fogh US, Nielsen HH, Olesen HP. Salicylate- and aspirin-induced uncoupling of oxidative phosphorylation in mitochondria isolated from the mucosal membrane of the stomach. Scand J Clin Lab Invest. 1976 Nov;36(7):649-654.
7. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet. 1984 Jun;1(8390):1311-1315.
8. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. Clin Microbiol Rev. 2006 Jul;19(3):449-490.
9. Hoogerwerf WA, Pasricha PJ. Agents used for control of gastric acidity and treatment of peptic ulcers and gastro-esophageal reflux disease. in The Pharmacological Basis of Therapeutics, JG Hardman, LE Limbird and GA Goodman, 10th Eds. 2001:1005–1019), New York, NY, USA McGraw-Hill.
10. Trust TJ, Alm RA, Pappo J. Helicobacter pylori: today's treatment, and possible future treatment. Eur J Surg Suppl. 2001;(586):82-88.
11. Lanas A, García-Rodríguez LA, Arroyo MT, Gomollón F, Feu F, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut. 2006 Dec;55(12):1731-1738.
12. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs. N Engl J Med. 1999 Jun;340(24):1888-1899.
13. Lichtenberger LM, Zhou Y, Dial EJ, Raphael RM. NSAID injury to the gastrointestinal tract: evidence that NSAIDs interact with phospholipids to weaken the hydrophobic surface barrier and induce the formation of unstable pores in membranes. J Pharm Pharmacol. 2006 Nov;58(11):1421-1428.
14. Lichtenberger LM, Barron M, Marathi U. Association of phosphatidylcholine and NSAIDs as a novel strategy to reduce gastrointestinal toxicity. Drugs Today (Barc). 2009 Dec;45(12):877-890.
15. Lenard M, Lichtenberger, Melisa B, Upendra M. Association of phosphatidylcholine and nsaids as a novel strategy to reduce gastrointestinal toxicity. Drugs Today (Barc). 2009 Dec;45(12):877-890.
16. Barrios JM, Lichtenberger LM. Role of biliary phosphatidylcholine in bile acid protection and NSAID injury of the ileal mucosa in rats. Gastroenterology. 2000 Jun;118(6):1179-1186.
17. Fiorucci S, de Lima OM, Jr Mencarelli A. Cyclooxygenase-2-derived lipoxin A4 increases gastric resistance to aspirin-induced damage. Gastroenterology. 2002 Nov;123(5):1598–1606.

18. Davies NM, Roseth AG, Appleyard CB, Mcknight W, Del Soldato P, et al. NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects. Aliment Pharmacol Ther. 1997 Jul;11(1):69-79.
19. Takeuchi, K, Suzuki, K., Yamamoto, H. Cyclooxygenase-2 Selective and Nitric Oxide-Releasing Nonsteroidal Anti-Inflammatory Drugs and Gastric Mucosal Responses. J Physiol Pharmacol. 1998a;49(4):501-513.
20. Fiorucci S, Antonelli E, Santucci L, Morelli O, Miglietti, et al. Gastrointestinal safety of nitric oxide–derived aspirin is related to inhibition of ICE-like cysteine proteases in rats. Gastroenterology. 1999a May;116(5):1089–1106.
21. Bertrand V, Guimbaud R, Sogni P, Lamrani A, Mauprivaz C, et al. Role of tumour necrosis factor-α and inducible nitric oxide synthase in the prevention of nitro-flurbiprofen small intestine toxicity. European Journal of Pharmacology. 1998 Sep;356(2-3):245–253.
22. Wallace JL, Reuter B, Cicala C, McKnight W, Grishsm MB. Novel nonsterodial anti-inflammatory drug derivatives with markedly reduced ulcerogenic properties in the rat. Gastroenterology. 1994 Jul;107(1):173-179.
23. Ukawa H, Yamakuni H, Shinichi K, Takeuchi. Effects of Cyclooxygenase-2 Selective and Nitric Oxide-Releasing Nonsteroidal Anti-inflammatory Drugs on Mucosal Ulcerogenic and Healing Responses of the Stomach. Digestive Diseases and Sciences. 1998;43(9):2003 -2011.
24. Marshall M, Moore PK. Effect of nitric oxide releasing paracetamol and flurbiprofen on cytokine production in human blood. European Journal of Pharmacology. 2004 Jan;483(2-3):317-322.
25. Goubern M, Andriamihaja M, Nübel T, Blachier F, Bouillaud F. Sulfide, the first inorganic substrate for human cells. FASEB J. 2007 Jun;21(8):1699-1706.
26. Fiorucci S, Orlandi S, Mencarelli A, Caliendo G, Santagada V, et al. Enhanced activity of hydrogen sulphide releasing derivative of Mesalamine (ATB-429) in a mouse model of colitis. Br J Pharmacol. 2007 Apr;150(8):996-1002.
27. Sobala GM, Pignatelli B, Schorah CJ, Bartsch H, Sanderson M, et al. (1991). Levels of nitrite, nitrate, N-nitroso compounds, ascorbic acid and total bile acids in gastric juice of patients with and without precancerous conditions of the stomach. Carcinogenesis. 1991 Feb;12(2):193-198.
28. Pohle T, Brzozowski T, Becker JC, Van der Voort IR, Markmann A, et al. Role of reactive oxygen metabolites in aspirin-induced gastric damage in humans: gastro protection by vitamin C. Aliment Pharmacol Ther. 2001 May;15(5):677-687.
29. Becker JC, Grosser N, Boknik P, Schröder H, Domschke W, et al. Gastroprotection by vitamin C a heme oxygenase-1 dependent mechanism? Biochem Biophys Res Commun. 2003 Dec;312(2):507-512.
30. Guo JS, Cho CH, Wang WP, Shen XZ, Cheng CL, et al. Expression and activities of three inducible enzymes in the healing of gastric ulcers in rats. World J Gastroenterol. 2003 Aug;9(8):1767-1771.
31. Jovanovic DV, Fernandes JC, Martel-Pelletier J, Jolicoeur FC, Reboul P, et al. In vivo dual inhibition of cyclooxgenase and lipoxygenase by ML-3000 reduces the progression of experimental osteoarthritis: suppression of collagenase 1 and interleukin-1 beta synthesis. Arthritis Rheum. 2001 Oct;44(10):2320-2330.
32. Brune K. Safety of anti-inflammatory treatment—new ways of thinking. Rheumatology. 2004 Feb;43(Suppl. 1):i16–i20.
33. Reginster JY, Bias P, Buchner A. First clinical results of licofelone (ML3000), an inhibitor of COX-1, COX-2 and 5-LOX, for the treatment of osteoarthritis. Annals of Rheumatic Diseases. 2002 Jun;61(Suppl.):116S.
34. Buchner A, Bias P, Lammerich A. Twice the therapeutic dose of licofelone – an inhibitor of COX-1, COX-2 and 5-LOX – results in a significantly lower gastrointestinal ulcer incidence than naproxen in osteoarthritis patients, when administered with or without concomitant low-dose aspirin. Annals of Rheumatic Diseases. 2003;62.
35. Guyton AC. Textbook of Medical physiology. 11th Edition. Elsevier saunder. 2005 Jul;821.
36. Hiraishi H, Tadahito S, Naomi W, Yukio O, Motoya E, et al. Polaprezinc protects gastric mucosal cells from noxious agents through antioxidant properties in vitro. Aliment Pharmacol Ther. 1999 Feb;13(2):261-269.
37. Shibata H. Clinical phase I study of Z-103. Clinical Pharmacology. 1992;20(1):149–163.
38. Graham DY, Malaty HM, Evans DG, Evans DJ Jr, Klein PD, et al. Epidemiology of Helicobacter pylori in an asymptomatic population in the United States. Effect of age, race, and socioeconomic status. Gastroenterology. 1991 Jun;100(6):1495-1501.
39. Rupnow MF, Shachter RD, Owens DK, Parsonnet J. Quantifying the population impact of a prophylactic Helicobacter pylori vaccine. Vaccine. 2001 Dec;20(5-6):879-885.
40. Lee CK, Soike K, Hill J, Georgakopoulos K, Tibbitts T. et al. Immunization with recombinant Helicobacter pylori urease decreases colonization levels following experimental infection of rhesus monkeys. Vaccine. 1999 Mar;17(11-12):1493-1505.
41. Lee A, Fox JG, Otto G, Murphy J. Small animal model of human Helicobacter pylori active chronic gastritis. Gastroenterology. 1990 Nov;99(5):1315-1323.
42. Blanchard TG, Nedrud JG. In Helicobacter pylori in the 21st century. Sutton P, Mitchell H, 1st ed. 2010;167-190.
43. Michetti P, Kreiss C, Kotloff KL, Porta N, Blanco J, et al. Oral immunization with urease and Escherichia coli heat-labile enterotoxin is safe and immunogenic in Helicobacter pylori-infected adults. Gastroenterology. 1999 Apr;116(4):804-812.
44. Ghiara P, Rossi M, Marchetti M, Di Tommaso A, Vindigni C, et al. Therapeutic intra gastric vaccination against Helicobacter pylori in mice eradicates an otherwise chronic infection and confers protection against reinfection. Infect Immun. 1997 Dec;65(12):4996-5002.
45. DeLyria ES, Redline RW, Blanchard TG. Vaccination of mice against H. pylori induces a strong Th-17 response and immunity that is neutrophil dependent. Gastroenterology. 2009 Jan;136(1):247-256.
46. Aebischer T, Bumann D, Epple HJ, Metzger W, Schneider T. Correlation of T cell response and bacterial clearance in human volunteers challenged with Helicobacter pylori revealed by randomised controlled vaccination with Ty21a- based Salmonella vaccines. Gut. 2008 Aug;57(8):1065-1072.
47. Benini S, Rypniewski WR, Wilson KS, Mangani S, Ciurli S. Molecular details of urease inhibition by boric acid: insights into the catalytic mechanism. J Am Chem Soc. 2004 Mar;126(12):3714-3715.
48. Mobley HLT, Mendz GL, Hazell SL. *Helicobacter pylori*: Physiology and Genetics. Washington (DC): ASM Press; 2001.
49. Weeks DL, Eskandari S, Scott DR, Sachs G (2000). H+-gated urea channel: The link between Helicobacter pylori urease and gastric colonization. Science. 2000 Jan;287(5452):482-485.
50. Li HX, Mao XH, Shi Y, Ma Y, Wu YN, et al. Screening and identification of a novel B-cell neutralizing epitope from Helicobacter pylori UreB. Vaccine. 2008 Dec;26(52):6945-6949.S
51. Kolkman JA, Law DA. Nanobodies from llamas to therapeutic proteins. Drug Discov Today Technol. 2010 Summer;7(2):e95-e146.
52. Spinelli S, Frenken LG, Hermans P, Verrips T, Brown K, et al. (2000). Camelid heavy-chain variable domains provide efficient combining sites to haptens. Biochemistry. 2000 Feb;39(6):1217-1222.
53. Malekshahi ZV, Gargari SL, Rasooli I, Ebrahimizadeh W. Treatment of Helicobacter pylori infection in mice with oral administration of egg yolk-driven anti- UreC immunoglobulin. Microb Pathog. 2011 Nov;51(5):366-372.

54. Reiche N, Jung A, Brabletz T, Vater T, Kirchner T, et al. Generation and characterization of human monoclonal scFv antibodies against Helicobacter pylori antigens. Infect Immun. 2002 Aug;70(8):4158-4164.

55. Chames P, Van Regenmortel M, Weiss E, Baty D. Therapeutic antibodies: successes, limitations and hopes for the future. Br J Pharmacol. 2009 May;157(2):220–233.

56. Wu Y, Zou Q, Luo P, Guo G, Wang X. Preparation of anti–{\ sl Helicobacter pylori} UreB monoclonal antibody and the detection of the ability of inhibition the urease activity. Journal of Immunology. 2005 Jan;21(5):393-396.

57. Ardekani LS, Gargari SL, Rasooli I, Bazl MR, Mohammadi M, et al. A novel nanobody against urease activity of Helicobacter pylori. Int J Infect Dis. 2013 Sep;17(9):e723-728.

58. Lauwereys M, Arbabi Ghahroudi M, Desmyter A, Kinne J, Hölzer W, E. et al. (1998). Potent enzyme inhibitors derived from dromedary heavy-chain antibodies. EMBO J. 1998 Jul;17(13):3512-3520.

59. Sonnenberg, A.(1994). Peptic ulcer. In: Digestive diseases in the United States: Epidermiology and Impact. US. Department of Health and Human Services, Public Health Services, National Institutes of Health. 1994:359-408; NIH publication no. 94-1447.

60. Murthy S, Goetz M, Hoffman A, Kiesslich R. Novel colonoscopic imaging. Clin Gastroenterol Hepatol. 2012 Sep;10(9):984–987.

61. Sauk J, Hoffman A, Anandasabapathy S, Kiesslich R. High-definition and filter-aided colonoscopy. Gastroenterol Clin North Am. 2010 Dec;39(4):859-881.

62. Jung M, Kiesslich R. Chromoendoscopy and intravital staining techniques. Baillieres Best Pract Res Clin Gastroenterol. 1999;13(1):11-19.

63. Rembacken BJ, Fujii T, Cairns A, Dixon MF, Yoshida S, et al. Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. Lancet. 2000 Apr;355(9211):1211-1214.

64. Hoffman A, Basting N, Goetz M, Tresch A, Mudter J, et al. High-definition endoscopy with i-Scan and Lugol's solution for more precise detection of mucosal breaks in patients with reflux symptoms. Endoscopy. 2009 Feb;41(2):107-112.

65. Mayinger B, Jordan M, Horner P, Gerlach C, Muehldorfer S, et al. Endoscopic light-induced autofluorescence spectroscopy for the diagnosis of colorectal cancer and adenoma. J Photochem Photobiol B. 2003 Apr;70(1):13-20.

66. van den Broek FJ, Fockens P, Van Eeden S, Kara MA, Hardwick JC, et al. Clinical evaluation of endoscopic trimodal imaging for the detection and differentiation of colonic polyps. Clin Gastroenterol Hepatol. 2009 Mar;7(3):288-295.

67. Goetz M, Wang TD. Molecular imaging in gastrointestinal endoscopy. Gastroenterology. 2010 Mar;138(3):828-833.e1.